ANTIVIRAL ACTIVITY AND RESOLUTION OF 2-HYDROXYMETHYL-5-(5-FLUOROCYTOSIN-1-YL)-1,3-OXATHIOLANE

This application is a Continuation application of U.S. Ser. No. 07/831,153, filed on Feb. 12, 1992 now abandoned, by Dennis C. Liotta, Raymond F. Schinazi, and Woo-Baeg Choi for "Antiviral Activity and Resolution of 2-Hydroxymethyl-5(5-Fluorocytosin-1-yl)-1,3-Oxathiolane" which is a continuation-in-part application of (1) U.S. Ser. No. 07/659,760, now U.S. Pat. No. 5,210,085, entitled "Method for the Synthesis, Compositions and Use of 2'-Deoxy-5-Fluoro-3'-Thiacytidine and Related Compounds", filed on Feb. 22, 1991, by Dennis C. Liotta, Raymond F. Schinazi, and Woo-Baeg Choi, which is a continuation in part application of U.S. Ser. No. 07/473,318, now U.S. Pat. No. 5,204,466, entitled "Method and Compositions for the Synthesis of BCH-189 and Related Compounds", filed on Feb. 1, 1990, by Dennis C. Liotta and Woo-Baeg Choi and, (2) a continuation-in-part of U.S. Ser. No. 07/736,089, now abandoned, entitled "Method of Resolution and Antiviral Activity of 1,3-Oxathiolane Nucleoside Enantiomers" filed on Jul. 26, 1991, by Dennis C. Liotta, Raymond F. Schinazi, and Woo-Baeg Choi, which is a continuation-in-part of U.S. Ser. No. 07/659,760, now U.S. Pat. No. 5,210,085, referenced above.

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BACKGROUND OF THE INVENTION

This invention is in the area of biologically active nucleosides, and specifically includes antiviral compositions that include 2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane ("FTC"), its physiologically acceptable derivative, or physiologically acceptable salt, and a method for the resolution and use of the (−)-β-L and (+)-β-D enantiomers of FTC.

In 1981, acquired immune deficiency syndrome (AIDS) was identified as a disease that severely compromises the human immune system, and that almost without exception leads to death. In 1983, the etiological cause of AIDS was determined to be the human immunodeficiency virus (HIV). By December of 1990, the World Health Organization estimated that between 8 and 10 million people worldwide were infected with HIV, and of that number, between 1,000,000 and 1,400,000 were in the U.S.

In 1985, it was reported that the synthetic nucleoside 3'-azido-3'-deoxythymidine (AZT) inhibits the replication of human immunodeficiency virus. Since then, a number of other synthetic nucleosides, including 2',3'-dideoxyinosine (DDI), 2',3'-dideoxycytidine (DDC), 3'-fluoro-3'-deoxythymidine (FLT), and 2',3'-dideoxy-2',3'-didehydrothymidine (D4T), have been proven to be effective against HIV. A number of other 2',3'-dideoxynucleosides have been demonstrated to inhibit the growth of a variety of viruses in vitro. It appears that, after cellular phosphorylation to the 5'-triphosphate by cellular kinases, these synthetic nucleosides are incorporated into a growing strand of viral DNA, causing chain termination due to the absence of the 3'-hydroxyl group.

The success of various 2',3'-dideoxynucleosides in inhibiting the replication of HIV in vivo or in vitro has led a number of researchers to design and test nucleosides that

substitute a heteroatom for the carbon atom at the 3'-position of the nucleoside. Norbeck, et al., disclose that (±)-1-[(2β, 4β)-2-(hydroxymethyl)-4-dioxolanyl]thymine (referred to as (±)-dioxolane-T) exhibits a modest activity against HIV (EC_{50} of 20 μm in ATH8 cells), and is not toxic to uninfected control cells at a concentration of 200 μM. *Tetrahedron Letters* 30 (46), 6246, (1989). European Patent Application Publication No. 0 337 713 and U.S. Pat. No. 5,041,449, assigned to IAF BioChem International, Inc., disclose 2-substituted-4-substituted-1,3-dioxolanes that exhibit antiviral activity.

U.S. Pat. No. 5,047,407 and European Patent Application Publication No. 0 382 526, also assigned to IAF Biochem International, Inc. disclose a number of 2-substituted-5-substituted-1,3-oxathiolane nucleosides with antiviral activity, and specifically report that the racemic mixture (about the C4'-position) of the C1'-β isomer of 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (referred to below as (±)-BCH-189) has approximately the same activity against HIV as AZT, and no cellular toxicity at the tested levels. (±)-BCH-189 has also been found to inhibit the replication of AZT-resistant HIV isolates in vitro from patients who have been treated with AZT for longer than 36 weeks.

Another virus that causes a serious human health problem is the hepatitis B virus (referred to below as "HBV"). HBV is second only to tobacco as a cause of human cancer. The mechanism by which HBV induces cancer is unknown, although it is postulated that it may directly trigger tumor development, or indirectly trigger tumor development through chronic inflammation, cirrhosis, and cell regeneration associated with the infection.

After a two to six month incubation period in which the host is unaware of the infection, HBV infection can lead to acute hepatitis and liver damage, that causes abdominal pain, jaundice, and elevated blood levels of certain enzymes. HBV can cause fulminant hepatitis, a rapidly progressive, often fatal form of the disease in which massive sections of the liver are destroyed.

Patients typically recover from acute hepatitis. In some patients, however, high levels of viral antigen persist in the blood for an extended, or indefinite, period, causing a chronic infection. Chronic infections can lead to chronic persistent hepatitis. Patients infected with chronic persistent HBV are most common in developing countries. By mid-1991, there were approximately 225 million chronic carriers of HBV in Asia alone, and worldwide, almost 300 million carriers. Chronic persistent hepatitis can cause fatigue, cirrhosis of the liver, and hepatocellular carcinoma, a primary liver cancer.

In western industrialized countries, high risk groups for HBV infection include those in contact with HBV carriers or their blood samples. The epidemiology of HBV is very similar to that of acquired immune deficiency syndrome, which accounts for why HBV infection is common among patients with AIDS or AIDS-related complex. However, HBV is more contagious than HIV.

A human serum-derived vaccine has been developed to immunize patients against HBV. While it has been found effective, production of the vaccine is troublesome because the supply of human serum from chronic carriers is limited, and the purification procedure is long and expensive. Further, each batch of vaccine prepared from different serum must be tested in chimpanzees to ensure safety. Vaccines have also been produced through genetic engineering. Daily treatments with a-interferon, a genetically engineered